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Dated: August 9, 2010
Electronic Signature for Meaghan L. Richmond: /Meaghan L. Richmond/

Docket No. 117825-05603
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Wingard *et al.*

Application No.: 10/509,627

Confirmation No.: 2806

Filed: April 29, 2005

Art Unit: 1612

For: PHARMACEUTICAL COMPOSITIONS CONTAINING WATER-SOLUBLE PRODRUGS OF PROPOFOL AND METHODS OF ADMINISTERING THE SAME

Examiner: D.C. Sutton

Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF TO THE EXAMINER'S ANSWER

Pursuant to 37 C.F.R. §41.41, Appellants submit this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer to Appellant's Brief (hereinafter "the Examiner's Answer") mailed from the U.S. Patent and Trademark Office on June 9, 2010.

STATUS OF THE CLAIMS

Claims 12, 13 and 36-39 are pending and stand rejected. Claims 14-19 are withdrawn. Claims 1-11 and 20-35 are canceled.

Appellants hereby appeal the rejection of claims 12, 13 and 36-39.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 12, 13 and 36-39 stand rejected under 35 U.S.C. §103(a) over Stella *et al.* (U.S. Patent No. 6,204,257, hereinafter "Stella") in view of Lowrie *et al.* ("The pediatric sedation unit: a mechanism for pediatric sedation," Pediatrics. 1998 Sep;102(3):E30, hereinafter "Lowrie").

ARGUMENTS

At pages 6-7 of the Examiner's Answer, the Examiner alleges that "Stella teaches the dosage, mode and schedule of administration of a compound of this invention are not particularly restricted" and that "Stella teach that substantially the same prodrug of propofol in substantially the same amounts, *i.e.* 0.5 mg/kg to 10 mg/kg…is administered parenterally." The Examiner relies on Lowrie as teaching "the amounts of propofol used in bolus administration to children…" Therefore, the Examiner concludes that "[i]t would have been reasonably expected that these amounts of prodrug could be delivered in a bolus parenteral injection; especially with the knowledge of the disclosure of Lowrie that propofol is delivered in a bolus injection for producing sedation in children."

Appellants respectfully disagree with the Examiner. From the outset, Appellants remind the Examiner that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results ***would have been predictable to one of ordinary skill in the art.*** (MPEP §2143.01 (III), citing *KSR International Co. v. Teleflex*, 398, 82 USPQ 2d 1385, 1396 (2007)). Appellants note that neither Stella nor Lowrie, alone or in proper combination, provide the required predictability that a bolus dose of fospropofol (*e.g.*, the propofol prodrug) would have such different pharmacokinetics from propofol (*e.g.*, Diprivan®) that it would be safe for administration to induce conscious sedation, as set forth in detail below.

First, at page 9 of the Examiner's Answer, the Examiner points to Figure 1; column 35, lines 47-52; and column 36, lines 1-5 of Stella for teaching that

> fospropofol was converted *in vivo* to propofol via phosphatase; and the production of propofol was delayed.

Appellants respectfully note that the Examiner's conclusions regarding Figure 1 and the experiment set forth at column 35, lines 47-52 and column 36, lines 1-5 of Stella are incorrect. Specifically, Figure 1 of Stella, shown below, illustrates the results of the ***in vitro*** conversion of the propofol prodrug to propofol, which was performed at pH 10.4 (*e.g.*, non-physiological pH) (*see* column 35, lines 57-59). This data merely demonstrate that the propofol prodrug is a substrate for alkaline phosphatase (*see* Stella, column 36, lines 3-5).

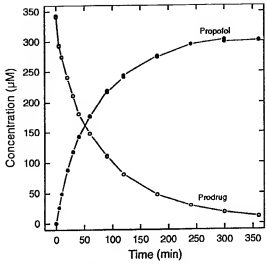

Figure 1 of Stella

In contrast, Figure 2 of Stella, shown below, provides the results of an ***in vivo pharmacokinetic comparison*** of Diprivan® (*e.g.*, propofol) and propofol obtained from the fospropofol. As disclosed in Stella (see column 37, lines 32-34), ***"the propofol blood levels resulting from the injection of the propofol prodrug approximate those from the injection of Diprivan®."*** Indeed, from Figure 2 of Stella, the plasma concentration of propofol derived from the prodrug after 1400 minutes appears ***higher*** than the concentration of Diprivan®.

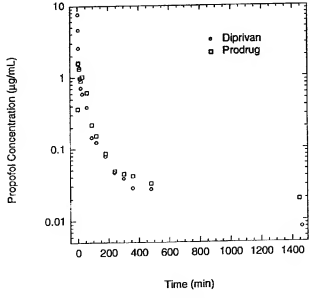

Figure 2 of Stella

Accordingly, despite the Examiner's conclusions to the contrary, one of skill in the art in possession of Stella at the time the present invention was made would have understood that fospropofol had a pharmacokinetic profile similar to that of Diprivan®, and further, that a greater amount of propofol derived from fospropofol appeared to remain in the plasma compared to Diprivan® over time.

While the Examiner relies on Lowrie for teaching the use of a slow bolus of propofol (*e.g.*, 1 to 2 mg/kg) for the sedation of children, Appellants respectfully submit that one of skill in the art and familiar with propofol would be aware of the serious cardiorespiratory side effects associated with the administration of a bolus dose of proprofol. In this regard, Appellants respectfully redirect the Examiner's attention to the FDA approved label of Diprivan® (*e.g.*, propofol). Throughout the label, the label teaches the safety risks associated with the administration of a bolus dose of Diprivan® and cautions against using bolus dosing for various age groups and sedation types. For example:

- for monitored anesthesia care: "slow infusions or slow injection techniques are preferable over rapid bolus administration…"
- for the elderly, debilitated, or ASA III/IV patients: "rapid (single or repeated) bolus dose should not be used for MAC sedation…"
- "[u]ndesirable side effects such as cardiorespiratory depression are likely to occur at high blood concentrations which result from bolus dosing…"
- "[a] rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation."
- for mechanically ventilated adult patients: "sedation should be initiated slowly with a continuous infusion in order to…minimize hypotension."

Indeed, even Lowrie acknowledges the complications of propofol, including that a

> decrease in blood pressure or widening of pulse pressure is a common and expected complication with use of propofol, the most frequently used drug in the

> PSU. Anesthesia induction with propofol was associated with a 20% to 40% decrease in blood pressure in 43.8% of patients in one study.

Lowrie also notes that the "extensive use of propofol for pediatric sedation" was "unusual outside the operating room or intensive care unit."

In view of the foregoing, Appellants respectfully submit that one of skill in the art, despite Lowrie's teachings regarding the administration of proprofol, would not have been able to predict that a bolus dose of fospropofol would be safe in view of the ***similar pharmacokinetic profile of fospropofol and propofol*** as taught by Stella in Figure 2 and ***the serious cardiorespiratory side effects*** described in the FDA label for propofol. In this case, Appellants submit that a skilled artisan would more strongly consider the FDA's warnings against using a bolus dose of propofol rather than a journal article which acknowledges the dangers of propofol and the unusual use of the drug, yet administers a "slow bolus" despite the FDA warnings.

Further, at page 8 of the Examiner's Answer, the Examiner asserts that "determining the concentration profiles would be within the purview of one of skill in the art" and that "...one of skill in the art of anesthesia will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering the compound..." The Examiner further alleges on page 9 of the Examiner's Answer that "[t]he studies carried out by Dr. Shah for the Declaration are not novel methods" and that "determining the concentration profiles of the drugs is routine and art recognized."

Appellants respectfully direct the Examiner's attention to MPEP 2143.01(IV), which states that "mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie obviousness" and that "[a] statement that modification of the prior art would have been 'well within the ordinary skill of the art at the time the claimed invention was made'...is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references." (*Ex parte Levengood*, 28 USPQ 2d 1300 (Bd. Pat. App. & Inter. 1993). Appellants note that the aforementioned statements are merely conclusory and that the Examiner provides no objective reason to combine the teachings of Stella and Lowry to arrive at the claimed invention.

Moreover, Appellants note that whether the experimentation to determine the concentration profiles or the protocol for administering the compound is undue or not novel is not relevant to the issue of the obviousness of the present invention. Rather, the issue is whether one of skill in the art, with the knowledge of the serious side effects of a bolus dose of propofol, as indicated on the FDA label, and the teachings of Stella that the *in vivo* pharmacokinetics of propofol derived from fospropofol were similar to that of Diprivan®, would have predicted that a bolus dose of fospropofol would have the pharmacokinetic profile demonstrated in the Shah Declaration. Indeed, with the serious side effects associated with a bolus administration of Diprivan® and the similar plasma concentrations shown in Stella, one of skill in the art would have not had any reasonable expectation that a bolus administration of fospropofol would be a successful protocol for administration of the drug.

With respect to the Declaration by Dr. Shah (hereinafter "the Shah Declaration"), the Examiner asserts at page 9 of the Examiner's Answer that

> one of ordinary skill in the art would readily be aware of the clearance of propofol from the body and ***would reasonably assume that some fospropofol is also cleared from the body before conversion.*** One would reasonably expect that the maximum concentration of propofol derived from the fospropofol would be less than from propofol, since both the parent and the prodrug are cleared from the body, and that the maximum concentration would occur at a latter [sic] time. (Emphasis added)

Appellants respectfully submit that the Examiner is using impermissible hindsight based on the Shah Declaration to conclude that the claimed invention is obvious. While one of skill in the art may have been aware of the clearance from the body of propofol, ***Stella provides no evidence that fospropofol also clears the body before conversion to propofol***, as asserted by the Examiner, and, in fact, does not even mention the rate of clearance of fospropofol. Further, one of skill in the art would have understood that even slight modifications in the chemical structure of a drug can yield significant changes in metabolism and would not have assumed that clearance of fospropofol ***before conversion*** would be similar to that of propofol. Indeed, the Examiner, at pages 10-11 of the Examiner's Answer, acknowledges that "fospropofol…is a distinct drug with a distinct plasma concentration of [sic] that of propofol…"

Regardless that Stella provides no evidence that fospropol clears the body before conversion to propofol and, in fact, states that the propofol blood levels resulting from the injection of the propofol prodrug approximate those from the injection of Diprivan®, the Examiner continues to use impermissible hindsight at pages 9-10 of the Examiner's Answer to reach the same conclusions set forth in the Shah Declaration by stating that:

> [s]ince the plasma concentration of propofol from the fosproprofol is lower, it would reasonably be expected that the degree of sedation produced by propofol derived from fospropofol would not be as deep as that for proprofol; and the sedation would reasonably be expected to wear off at a longer time, since fospropofol produces a maximum, yet lower, concentration at a later time than that of propofol.

Appellants respectfully submit that a skilled artisan would not have been able to reach the aforementioned conclusions by the teachings of Stella or Lowrie, alone or in proper combination, because neither reference teach or suggest that the clearance of fospropofol is the same as that of propofol, which is the basis of the Examiner's conclusions.

Finally, the Examiner contends at pages 11-12 of the Examiner's Answer that "[t]here is no data concerning the production of conscious sedation by bolus administration of the prodrug in amounts from 2 mg/kg to less than 5 mg/kg" and that "there is no data concerning the production of conscious sedation by bolus administration of the prodrug in amounts…which is greater than 10 mg/kg but less than 15 mg/kg." The Examiner concludes that "[t]he amounts are not commensurate with the scope of claim 12, which recites an amount of 2 mg/kg to less than 15 mg/kg." The Examiner further asserts that "Appellant provided no data in the Examples on the production of conscious sedation by the acid form of the prodrug or any other salt other than sodium."

Appellants respectfully direct the Examiner's attention to MPEP § 2145, which states that "[w]hen considering whether proffered evidence is commensurate in scope with the claimed invention, ***Office personnel should not require the applicant to show unexpected results over the entire range of properties*** possessed by a chemical compound or composition." See, *e.g.*, *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987). Indeed, MPEP §2145 goes on to state that "a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a *prima facie* case

of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.'" *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). Moreover, MPEP § 2145 states that "an exemplary showing may be sufficient to establish a reasonable correlation between the showing and the entire scope of the claim, when viewed by a skilled artisan." See, *e.g.*, *Chupp*, 816 F.2d at 646, 2 USPQ2d at 1439; *Clemens*, 622 F.2d at 1036, 206 USPQ at 296.

With respect to the amounts claimed in claim 12, Appellants submit that the evidence provided in the specification (*e.g.*, conscious sedation achieved at dosages of 5 mg/kg and 10 mg/kg) and the Shah Declaration (*e.g.*, conscious sedation achieved at 10 mg/kg) establish a reasonable correlation between the evidence and the entire scope of the claim. As in *In re Clemens*, Appellants respectfully submit that a skilled artisan would be able to extend the probative value of the trend in the data presented in the specification and the Shah Declaration to arrive at the claimed dosages.

With respect to the Examiner's assertions that Appellants have provided no data for the production of conscious sedation by other forms of fospropofol (*e.g.*, the acid for or other metal salts), Appellants distinguish the present case from *In re Grasselli*, 713 F.2d at 743, 218 USPQ at 778, cited by MPEP §2145. Specifically, the MPEP cites *In re Grasselli* as finding superior properties for sodium containing composition insufficient to establish the non-obviousness of broad claims for a catalyst with "an alkali metal" where it was well known in the catalyst art that different alkali metals were not interchangeable. In contrast, one of skill in the art at the time of the invention would have expected that the acid form of fosproprofol or fospropofol appended with different alkali metals would have had similar properties. Indeed, even the Examiner acknowledges that "Stella teaches the acid form and metal salt forms of substantially the same prodrug as the instant compound."

In view of the foregoing, Appellants respectfully submit that neither Stella nor Lowrie, alone or in proper combination, provide the required predictability that a bolus dose of fospropofol (*e.g.*, the propofol prodrug) would have such different pharmacokinetics from propofol (*e.g.*, Diprivan®) that it would be safe for administration to induce conscious sedation. Accordingly, Appellants respectfully request reversal of the rejection of the claims under 35 U.S.C. §103.

Dated: August 9, 2010

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